Role of a ZIKV CHIM in vaccine evaluation

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ZIKV congenital syndrome

- There is increasing evidence from ZIKV outbreak in Latin America that congenital ZIKV syndrome can occur regardless of the timing of maternal infection
- Severity of disease in the mother is not associated with the occurrence of ZIKV congenital syndrome in the infant (ZIKV congenital syndrome can occur regardless of whether or not the mother had a symptomatic ZIKV infection)
  - This may indicate any level of viremia in the mother may cause adverse outcomes in the fetus
  - ***Prevention of symptomatic illness in the mother may not be sufficient to prevent CZS in the fetus; prevention of infection may be required***

ZIKV CHIM in vaccine development

- Down-selection of candidate vaccines
  - Currently 45 candidate ZIKV vaccines have been described as under development
  - Limited financial and human resources are available to evaluate all these candidates
  - Down-select candidates **early** to ensure resources are utilized for development of candidates that demonstrate the highest likelihood of success
- ***Assess vaccine efficacy if circulation of ZIKV diminishes such that true field efficacy trials cannot be done***

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ZIKV CHIM in vaccine development

- Assess the ability to induce sterilizing immunity and its duration – very difficult to do in field studies
- Assess the effect of pre-existing flavivirus immunity on vaccine immunogenicity / protection
- Assess the ability of passively-transferred antibody to protect against ZIKV infection and the durability of that protection
- Identify correlate(s) of protection

Secondary advantages of a ZIKV CHIM

- Characterize ZIKV infection in humans
  - Determine how long ***replicating*** ZIKV is shed in blood, urine, semen, vaginal secretions to better determine the risk of sexual transmission
  - Determine if viral load affects duration of shedding
  - Determine if viral load affects symptom presentation
  - Determine if inoculum affects peak viral load/duration of shedding
- Data from well-designed ZIKV CHIM could be used in the development of public health guidelines related to transmission of ZIKV
- Characterize the effect of pre-existing DENV antibody (or other flavivirus antibody) on ZIKV infection

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ZIKV vaccines in development

	Developers	Type of vaccine	Antigen	Development/Phase	Registration No.
GLS-5700	GeneOne / Inovio	DNA	prM & E	Phase 1	NCT02809443, NCT02887482
VRC ZIKV DNA	VRC/NIAID	DNA	PrM & E	Phase 1	NCT02840487, NCT02996461, NCT03110770
	BioManguinhos/ Fiocruz	VLP	E protein	Non-clinical	
ZIKVLP	Institut Pasteur Shanghai	VLP		Non-clinical	
	NewLink Genetics	VLP	PrM & E	Non-clinical	
	Bharat	PIV	Whole virus		Phase 1 (registration # not known)
	BioManguinhos/ Fiocruz	PIV	Whole virus	Non-clinical	
Butantan ZIKV	Butantan	PIV	Whole virus	Non-clinical	
	NewLink Genetics	PIV	Whole virus	Non-clinical	
	Valneva	PIV	Whole virus	Non-clinical	

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ZIKV vaccines (con't)

	Developers	Type of vaccine	Antigen	Development/Phase	Registration No.
Butantan attenuated ZIKV	Butantan	LAV	Whole virus	Non-clinical	
rZIKV/DEN2Δ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
rZIKV/DEN4Δ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
rZIKV-3′/DEN4Δ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
rZIKVΔ30	NIAID Intramural	LAV	Whole virus	Non-clinical	
	Bharat	PIV	Whole virus	Non-clinical	
	BioManguinhos/ Fiocruz	PIV	Whole virus	Non-clinical	
Butantan ZIKV	Butantan	PIV	Whole virus	Non-clinical	
	NewLink Genetics	PIV	Whole virus	Non-clinical	
	Valneva	PIV	Whole virus	Non-clinical	
ZIKV PIV	WRAIR/Harvard/ NIAID/Sanofi Pasteur	PIV	Whole virus	Non-clinical	NCT02952833, NCT02937233, NCT02963909, NCT03008122

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ZIKV vaccines (con't)

	Developers	Type of vaccine	Antigen	Development/ Phase
	BioManguinhos/Fiocruz	Recombinant viral vector	PrM/E & NS1 proteins	Non-clinical
	BioManguinhos/Fiocruz	Recombinant viral vector	E protein	Non-clinical
GEO-ZM05	GeoVax/ UGA/CDC	Recombinant viral vector	PrME+NS1	Non-clinical
NI.LV-ZK	Institut Pasteur France	Recombinant viral vector	PrM/E	Non-clinical
ChAdOx1-Zk	Zika structural proteins	Recombinant viral vector		Non-clinical
Chimeravax-Zika	Sanofi Pasteur	Recombinant viral vector	Zika structural proteins	Non-clinical
SCV-CHIKV+ZIKV+YF	Sementis Ltd	Recombinant viral vector	ZIKV, CHIK, YF	Non-clinical
MV-Zika	Themis Bioscience GmbH	Recombinant viral vector	prM-E	NCT02996890
VXA-Zikavax	Vaxart	Recombinant viral vector	Env+	Non-clinical
Replikins Zika Vaccine	Replikins, Ltd and LLC	Peptide	Synthetic peptides	Non-clinical
mRNA-1325	Valera (Moderna)	mRNA	prM-E	NCT03014089

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Conclusions from an ethical review of Zika human challenge convened by US NIH December 2016

https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf

Key Question: Are the **risks reasonable, minimized, and justified** by the potential **social value** of the trial?

Conclusion:

- There is substantial uncertainty about the risks to potential volunteers in Zika virus human challenge study.
- Particular concern about possible risks to third parties (foetuses, members of the community)
- Absence of a strong argument and evidence that a challenge study will accelerate vaccine development
- Absence of an indication that field trials will be prohibitively difficult to conduct
- The committee concluded that it is premature to proceed with a Zika virus human challenge trial

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Ethics consultation – key misunderstandings

- Down selection of candidate ZIKV vaccines:
  - Did not appreciate the role of eliminating candidate vaccines from further development early

The committee had difficulty evaluating this type of rationale in the compressed schedule we had for decision-making. We heard evidence at the meeting that animal models and results in early phase trials could be sufficient to pick the best vaccine candidate. We also gathered some evidence on whether challenge studies have sped up vaccine approvals, based on other disease models, and we concluded that the evidence is mixed

- Cannot learn about ZIKV transmission, ZIKV infection
  - Focused heavily on maternal-fetal transmission
  - Did not recognize value of examining shedding of virus in semen or mosquito transmission

Although a Zika virus human CHIM is *not* the best way to learn more about the virus in terms of its effects on the body or the ways that it can be transmitted to others, learning about pathogenesis or early

Ethics consultation – key misunderstandings

- Efficacy outcomes of ZIKV vaccine trials
- "ZIKV disease would not work for a ZIKV CHIM"
  - Infection vs disease
  - Rash very common clinical sign
  - Do not need more pathogenic strain

very frequent testing. Although a WHO expert consultation suggested that clinical Zika virus disease should initially be the primary efficacy parameter for Zika vaccine trials,[86] this would not work for a Zika CHIM. Relying on disease as the primary outcome of a Zika CHIM would require developing strains that are more pathogenic than those isolated in recent outbreaks, since somewhere between 50-80% of people infected with Zika virus have no major symptoms.[87] This suggests that a challenge study could be uniquely able to develop

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Risks of ZIKV CHIM

- ZIKV illness
  - ZIKV infection is generally described as a mild transient illness with the most common physical sign/symptom being rash
- Congenital ZIKV syndrome if infected in utero
- Guillian-Barré syndrome or other reported neurological complications
- Transmission of ZIKV
  - Vector-borne transmission
  - Sexual transmission

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Sexual transmission of ZIKV

- CDC has confirmed 48 cases of sexual transmission
  - Only 1 case female-to-male
  - All but one of the travelers had symptoms consistent with ZIKV
- All cases of documented sexual transmission occurred within 21 days of return from ZIKV-endemic area
  - One case occurred ~ 40 days after return but both partners traveled to ZIKV-endemic area
- ***To date, there is only 2 prospective longitudinal studies that have evaluated ZIKV shedding in body fluids, including semen***
  - Very little data on infectious virus in semen
  - Only study to look at this found infectious ZIKV in 6/20 (30%)

Guillain-Barré Syndrome (GBS) and ZIKV

- Current CDC research suggests GBS is associated with ZIKV; however CDC states only a small proportion of people with recent ZIKV get GBS
- Most studies describing GBS and ZIKV are observational
- Onset of GBS following ZIKV quite early in many of these studies
- Diagnosis of ZIKV in many of these studies by history of rash/fever

GBS & ZIKV – Puerto Rico

- Overall, the number of persons with suspected GBS and evidence of ZIKV or flavivirus infection was 2.5 times greater than the number of persons with suspected GBS and no evidence of ZIKV infection
- Median interval from antecedent acute illness to onset of neurologic signs was 5 days (range 0 – 17 days)
- Median age of patients was 55 (range 21 – 88)
  - Higher incidence of women with GBS

Risk Mitigation in ZIKV CHIM

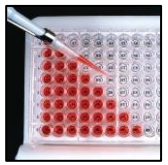
- Risk of congenital ZIKV syndrome
  - Pregnancy and breast-feeding would exclude participation
  - Pregnant partner would be exclusionary criterion
  - Mandatory use of highly effective contraception (oral or implantable hormonal, IUD)
- Risk of transmission
  - Conduct the study as an inpatient study (inpatient for about 14 days post-infection)
  - Educate subjects on the risk of sexual transmission
  - Require all subjects to agree to use barrier contraception for the duration of the study
  - Partners could be voluntarily monitored
- Risk of GBS (or other neurological complication)
  - Enroll younger subjects (≤ 40)
  - Ensure subjects are fully educated regarding the risk of GBS
  - Ensure diagnosis and treatment of GBS are available to all subjects
  - Indemnify trial such that subjects are not responsible for cost of care

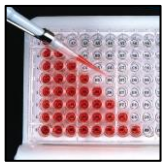
Controlled Human Infection Virus

1. Acute serum from uncomplicated Zika cases

2. Passage in qualified serum-free Vero cells (2X)

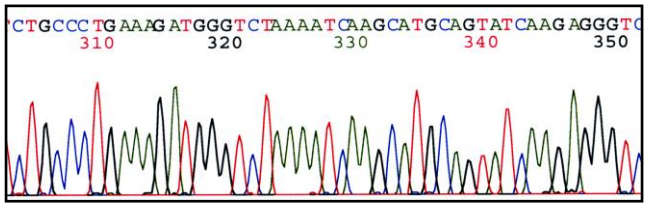
3. Terminal dilutions





4. Amplification in qualified serum-free Vero cells (2X)

5. Sequence



6. NHP evaluation

7. cGMP lot production

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Controlled Human Infection Virus

Primary serum for virus isolation

Nicaragua

ZIKV-Nicaragua/2016-5847
ZIKV-Nicaragua/2016-5242
ZIKV-Nicaragua/2016-7420
ZIKV-Nicaragua/2016-8385

Brasil - SP

ZIKV-Campinas/2016 (Transfusion)
ZIKV-SJRP/2016-116
ZIKV-SJRP/2016-184
ZIKV-SJRP/2016-190

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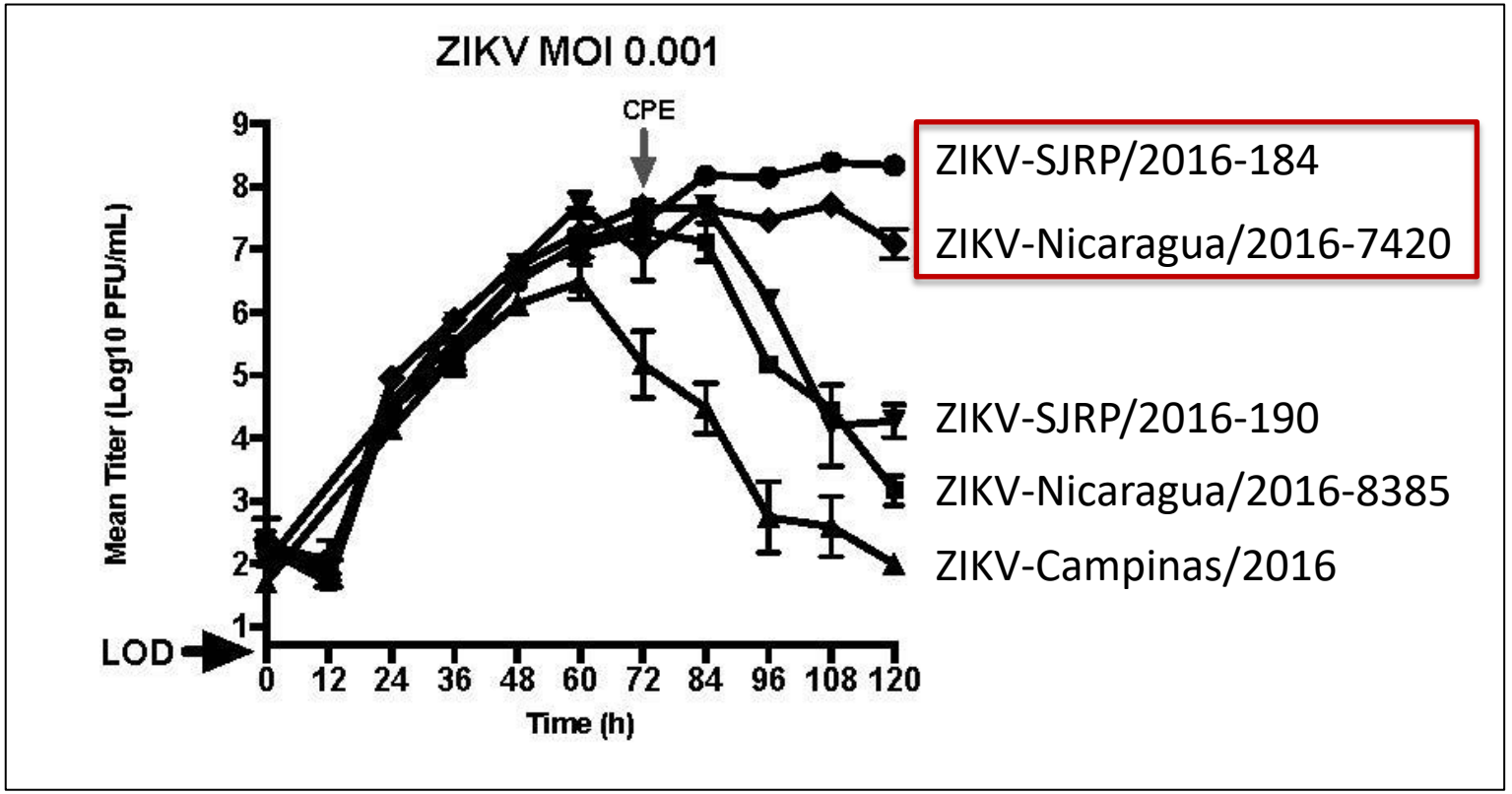
Controlled Human Infection Virus

Growth kinetics in Vero cells



cGMP manufacture is complete and safety/release testing is underway

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Summary

- ZIKV CHIM provides the opportunity to down-select candidate vaccines such that only those that meet specified efficacy criteria would proceed to larger field trials in endemic areas
  - Sterilizing immunity
  - Efficacy evaluation if unable to be done in the field
- ZIKV CHIM can be used to fully characterize the replication/shedding of ZIKV in humans
  - Possibly inform public health policy
- Risks associated with a ZIKV CHIM are being evaluated and scientific evidence suggests that risk mitigation will allow the study to proceed in a ***safe and ethical manner***
  - Narrow pathway forward